REMARKS

Status of the Claims

Claims 47, 58-61, 66-73, and 113-119 are pending. Claims 47, 58-61, 66-73, and 113-119 are rejected. Claims 47, 67 and 71-72 are amended herein. Claims 1-46, 48-57, 62-65, and 74-112 were canceled previously. Claims 60, 66, 70, and 113-114 are canceled herein. No new matter has been added.

Claim amendments

Claim 47 is amended to incorporate the limitations of claims 66, 70 and 113-114 and to replace "introducing" with "transducing" as reflective of the established method using adenoviral vectors. The preamble is amended to delete the phrase "that express an apoptosis-mediating receptor" as the claim now limits the cancer cells as expressing Fas receptor. Amended independent claim 47 now recites a method of inducing death in cancer cells by transducing the cancer cells with an adenoviral vector comprising a tissue-specific promoter and inducible promoter or an inducible promoter that controls the expression of Fas ligand. Claims 67 and 71-72 are amended to properly depend from amended claim 47. No new matter has been added in any amended claim.

Rejections Under 35 USC §112, 1st Paragraph

Claims 118 and 119 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The Examiner states that it is unclear whether the biological material recited in claims 118-119 is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public.

The constructs recited in claims 118 and 119 are Adv_{TET} and Ad/FasL-GFP_{TET}, respectively. All the vectors to produce Adv_{TET} and GFP_{TET} are identified in the specification and commercially available from Clontech and the FasL cDNA, the sequence of which can be obtained from Genbank, is in a Bluescript vector commercially available from Invitrogen (pg. 26, ll. 16-26).

A novel aspect of the Ad/FasL-GFP_{TET} is that it is a double recombinant adenoviral vector where the tet-responsive element and the transactivator element of Adv_{TET} are built into the opposite ends of the same vector (pg. 25, ll. 14-17; Fig. 1C). Generally, the construction of adenoviral vectors is known in the art and one of ordinary skill in the art would readily be able to obtain the materials to construct this vector. With the guidance provided in the specification and Figures (pg. 26, ll. 26 to pg. 27, ll. 29; pg. 30, ll. 1-23; Figs. 1B-1C), such artisan would be able to construct Ad/FasL-GFP_{TET} with the required placement of the tet-responsive element and the transactivator element. The assembly of Ad/FasL-GFP_{TET} particularly is detailed in Figure 1C.

Accordingly, in view of the arguments presented herein, Applicants respectfully request that the rejection of claims 118-119 under 35 USC §112, 1st paragraph be withdrawn.

Claims 47, 58-61, 66-73 and 113-119 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The Examiner states generally that the specification, while being enabled for *in vitro* use of apoptosis-mediated cancer cell death, does not reasonably provide enablement for *in vivo* use. The Examiner also states that the claims read on gene therapy and *in vivo* use. The Examiner makes the following points.

Scope/Breadth of the claims and Nature of the Invention

The Examiner states that the scope/breadth of the claims are broad; more particular claims are drawn to Fas/FasL for inducing apoptosis. The Examiner also states that the Fas/FasL apoptosis pathway is directed toward inducing death in cancer cells and read on *in vivo* use, i.e., eradication of cancerous cells in tumors in any subject. Applicants have amended independent claim 47, as discussed *supra*, to recite Fas/FasL.

State/Unpredictability of the art

The Examiner quotes various references in stating that "...there is still no conclusive evidence that gene-therapy protocol has been successful in the treatment of a human disease." (Anderson, *Nature*, 1998; 392:25-30, at 25) and that gene therapy or gene transfer may have unpredictable effects on cells (Check, *Nature*, 2003; 421:678; Juengst, *BMJ*, 2003: 326: 1410-11). The Examiner also states generally, with respect to Fas/FasL, that the state of the art is still developing with many substantial concerns and unresolved questions, particularly because (1) *in vivo* studies to date have been with immunocompromised mice (Arai et al, cited supra); (2) clinical studies of the therapeutic efficacy of FasL in killing cancer cells were disappointing due to "severe toxicity observed in preclinical studies" (Rossi and Gaidano, *Haematologica/J. Hematology*, 2003, 88(2): 212-18, at 217); (3) Fas receptors are widely expressed by many non-cancerous cells, FasL could have deleterious effects on normal cells expressing Fas receptor, e.g. hepatocytes, with even a base line level of or "leaky" expression of FasL; (4) if viral vectors enter the systemic system, with or without expressing FasL, they can be delivered to other cells exacerbating the immune response; such as tumor immune privilege occurring when intratumoral lymphocytes expressing Fas receptor are killed upon expression of FasL.

Applicants have canceled claims 60, 66, 70, and 113-114. Applicants invention, as recited in amended claim 47, requires that the cancer cells are transduced with an adenoviral vector comprising a tissue-specific

and/or inducible promoter to regulate FasL expression. In considering inducible promoters, the specification teaches that a novel double recombinant replication-deficient adenoviral vector is used to transduce the cancer cells to achieve tight control over FasL expression. The responsive element, e.g., Tet, and the transactivator element are built into the opposite ends of the same vector to avoid enhancer interference (pg. 25, ll. 9-17; pg. 33, ll. 25 to pg. 34, ll. 6). This allows the entire regulated expression system to be delivered in a single adenoviral vector with more efficient delivery to target cells with more uniform regulation of FasL expression and mimimizes background and/or unregulated expression of FasL (pg. 30, ll. 1-16; Figs. 1B-1C). For tissue-specific promoters, the specification teaches the construction of these adenoviral vectors using tissue-specific promoters with inducible promoters which also allows parenteral delivery of virus for treatment of metastatic disease (pg. 35, ll. 2-4).

Applicants also demonstrated that the Fas receptor blocking antibody did not prevent induction of apoptosis and that there is no intrinsic property of the adenovirus that facilitated induction of apoptosis (pg. 36, ll. 17-27). Most importantly, the specification teaches that Ad/FasL-GFP$_{TET}$ was administered to 14 mice without lethality to the mice, but where tumor cell growth is stopped or retarded (pg. 37, ll. 3-9). As such, Applicants respectfully draw the Examiner's attention to the Exhibit A provided in the Response filed May 24, 2004 demonstrating the effectiveness of an adenoviral vector encoding

FasL in induction of cancer cell death and tumor regression in breast cancer xenografts *in vivo*.

The use of tissue-specific promoters overcomes the problem of delivery to non-target cells with resultant adverse effects. Adenoviral vectors comprising inducible promoters may be delivered via infusion to or direct injection into the tumor or tumor cells, as is described in the instant specification and is known in the art to avoid toxic interactions with other cells. **Arai** *et al.* teach that direct injection of their ADV-FasL vector into the tumor mass appears to remain localized and does not give rise to toxicity, such as fulminant hepatitis (pg. 13864, end of PP).

In considering tumor immune privilege, the instant adenoviral vectors expressing FasL are used to induce cancer cell death. In that these vectors are localized to the cancer cells comprising the tumor, Applicants submit that any concomitant death of intratumor lymphocytes would also be localized without systemic repercussions.

Amount of guidance/working examples and experimentation

The Examiner states that the examples do not provide any significant guidance with respect to unpredictability in practicing the claimed invention in vivo in an immunocompetent subject such as in circumventing immunotoxicity and immunoneutralization that would be attendant with administration to human subjects or guidance with respect to the unpredictability of FasL expression in non-target cells. Furthermore, the

Examiner states that given such guidance is not provided, a skilled artisan would be required to conduct trial and error experimentation of an undue, unpredictable nature in order to practice the invention commensurate with the claims' scope.

Applicants reiterate the arguments presented *supra* addressing the Examiner's concerns. Applicants have provided ample guidance to construct the adenoviral vectors required for the practice of the invention and have demonstrated how the unique construction of said with particularly direct delivery thereof to cancer cells ~~with~~ التي induce cancer cell death without incurring or significantly minimalizing the adverse effects that might occur in a human subject. Applicants have demonstrated that such procedure is not lethal and induces cancer cell death.

With regard to the Examiner's statements as to the unpredictability of gene therapy in general and of the use of Fas/FasL in particular, Applicant submits that such unpredictability *per se* does not preclude the specification from enabling the instant invention. Applicant has amended the claims to recite a specific embodiment using Fas/FasL and has demonstrated that the adenoviral vectors used in the practice of the invention are designed specifically to avoid the possible negative consequences of Fas/FasL raised by the Examiner. Such demonstration enables Applicant's method of inducing death of cancer cells that express Fas receptor *in vitro* and *in vivo* by transducing the cancer cells to express FasL and, thus, should remove any basis the Examiner might have to doubt enablement.

Furthermore, in doing so, Applicant submits that such demonstration exceeds the standard for enablement because, as pointed out by the Examiner, these consequences primarily concern the safety and efficacy of practicing the invention. It is well established in patent law that usefulness, particularly of a therapeutic agent, may includes the expectation of further routine research and development. The stage at which this type of invention becomes useful is well before it is ready to be administered to humans. Applicant has met this standard. Accordingly, in view of the claim amendments and arguments presented, Applicant requests that the rejection of claims 47, 58-59, 61, 67-69, 71-73 and 115-119 under 35 USC §112 be withdrawn.

The Rejections Under 35 USC §102

Claims 47, 58-61 and 113-114 stand rejected under 35 USC §102(a) as anticipated by **Arai** *et al.* Claims 47, 58-61 and 115-116 are rejected under 35 USC §102(b) as anticipated by **Eicher** *et al.* This rejection is respectfully traversed.

The Examiner states that **Arai** *et al.* teach adenoviral mediated gene transfer into renal carcinoma cells which expresses Fas receptor to induce, particularly, an adenoviral vector encoding FasL to induce cell death. The Examiner states that **Eicher** *et al.* teach the same method using an adenoviral vector encoding p53, an apoptosis mediating ligand to induce cell death in cancer cells of head and neck origin.

Applicants have incorporated the limitations of claims 66, 70 and 113-114 into independent claim 47 and have canceled these claims. Amended claim 47 now recites the limitations of controlling expression of Fas ligand by a tissue-specific promoter or an inducible promoter in the adenoviral vector. Neither **Arai** *et al.* nor **Eicher** *et al.* teach this claim element and therefore cannot anticipate amended independent claim 47 nor claims 58-61 and 115-116 which depend directly or indirectly therefrom. Accordingly, Applicant respectfully requests that the rejection of claims 47, 58-61 and 113-116 under 35 USC §102(a)(b) be withdrawn.

This is intended to be a complete response to the Office Action mailed August 10, 2004. Applicant submits that claims 47, 58-59, 61, 67-69, 71-73 and 115-119 are in condition for allowance. If any issues remain, the please telephone the undersigned attorney for immediate resolution. Applicants include a Petition for a 3 Month Extension of Time. Please charge the $510 extension fee to the credit card identified on the enclosed Form PTO-2038. Please debit any insufficiency of fees from Deposit Account No. 07-1185.

Respectfully submitted,

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ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391 (tel.)
(713) 270-5361 (facs.)
badler1@houston.rr.com

Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant